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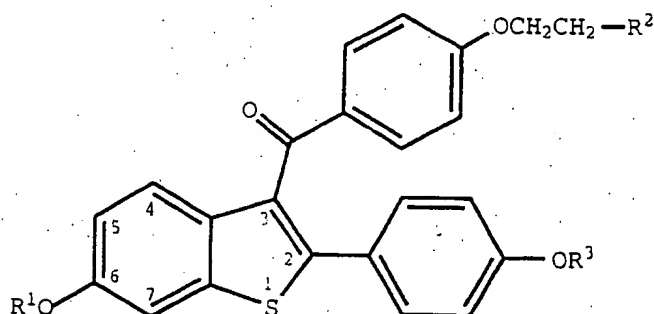
(71) Applicant: **ELI LILLY AND COMPANY**  
Lilly Corporate Center  
Indianapolis Indiana 46285 (US)

(72) Inventor: **Sales, James Joseph**  
9215 Behner Brook Drive  
Indianapolis, Indiana 46250 (US)  
Inventor: **Cullinan, George Joseph**  
Rural Route 1, Box 468  
Trafalgar, Indiana 46181 (US)

(74) Representative: **Tapping, Kenneth George et al**  
Lilly Industries Limited  
European Patent Operations  
Erl Wood Manor  
Windsor Surrey GU20 6PH (GB)

(54) **2-Phenyl-3-azoylthiophenes for inhibiting breast disorders.**

(57) A method of inhibiting breast disorders administering to a human in need of treatment an effective amount of a compound having the formula



(I)

wherein R<sup>1</sup> and R<sup>3</sup> are independently hydrogen, -CH<sub>3</sub>,

$\text{-C(=O)-C}_1\text{-C}_6\text{ alkyl}$ , or  $\text{-C(=O)-Ar}$ ,

wherein Ar is optionally substituted phenyl;

R<sup>2</sup> is selected from the group consisting of pyrrolidine, hexamethylenamino, and piperidino; or a pharmaceutically acceptable salt or solvate thereof.

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Jouvé, 18, rue Saint-Denis, 75004 Paris

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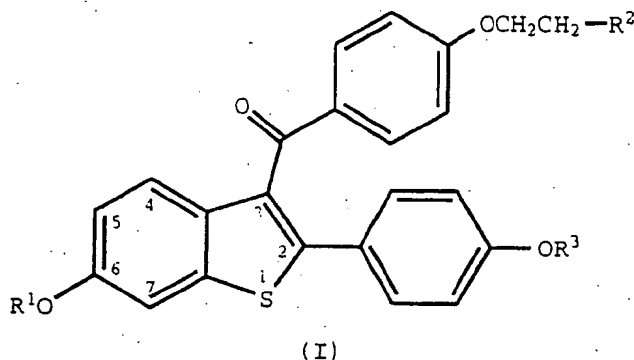
In the United States, one in every four women require medical attention for breast symptomatology. While much rarer, males also encounter breast disorders. Such disorders include galactorrhea, gynecomastia, hypertrophy, polythelia, mastodynia/mastalgia, hyperprolactinemia, and generally non-fibrocystic, non-cancerous mastopathias.

Breast pain is common and estimated to be present in 50% of women. Normally the etiology is unclear. The discomfort generally is classified as (1) cyclic mastalgia or mastodynia occurring immediately prior to the menses; (2) changes in the breast such as duct ectasia and sclerosing adenosis, or (3) referred pain such as costochondritis.

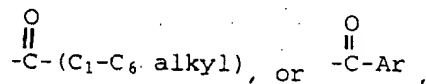
Gynecomastia is enlargement of the glandular breast tissue in male humans (the female counterpart is hypertrophy). This enlargement is localized to the aureoles and can be unilateral or more commonly bilateral. The condition is usually benign in nature; however it can be the source of severe psychological disturbance to the patient. Gynecomastia is most commonly found in males at the time of puberty, but can occur at any age. Gynecomastia can have many underlying causes, e.g., Klinefelter's syndrome (XXY chromosomal abnormality), liver disorders, estrogen therapy for prostatic carcinoma, tumors of various endocrine organs, and certain drugs (digitalis and Dilantin). The common relationship between all these causes and the resulting gynecomastia is the production of abnormal amounts of estrogens. Currently, treatment of this disease is limited to three therapies: 1) Determination and treatment of the underlying cause. 2) Surgical removal of the breast tissue. 3) Treatment with diethylstilbestrol and radiation. Determination and treatment of the underlying cause of gynecomastia is not always possible. Surgery and treatment with diethylstilbestrol and radiation is not always successful and entails great expense and risk. Clearly, a more effective and safer therapy would be useful.

Galactorrhea is the production of breast milk in the male or female when not immediately associated with pregnancy. The highly inappropriate and rare response in the male breast is accompanied by severe psychological discomfort to the male patient. It is thought to be caused by an overproduction of estrogen and prolactin excess. Surgical treatment is usually the therapy of choice if the underlying cause can not be determined or treated. A safer and less costly therapy would be useful.

This invention provides methods for inhibiting breast disorders comprising administering to a human in need of treatment an effective amount of a compound of formula I



wherein  $R^1$  and  $R^3$  are independently hydrogen,  $-CH_3$ ,



wherein Ar is optionally substituted phenyl;

$R^2$  is selected from the group consisting of pyrrolidino, hexamethylenelmino, and piperidino; and pharmaceutically acceptable salts and solvates thereof.

The current invention concerns the discovery that a select group of 2-phenyl-3-arylbenzothiophenes (benzothiophenes), those of formula I, are useful for inhibiting breast disorders. The methods of treatment provided by this invention are practiced by administering to a human in need a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit the breast disorder. Breast disorders include hyperprolactinemia, polythelia, gynecomastia, galactorrhea, and non-fibrocystic, non-can-

cerous mastodynia and mastopathy. The term inhibit is defined to include its generally accepted meaning which includes prophylactically treating a human subject to incurring the breast disorders described, and holding in check and/or treating existing disorders. As such, the present method includes both medical therapeutic and/or prophylactic treatment, as appropriate.

5     Raloxifene, a compound of this invention wherein it is the hydrochloride salt of a compound of formula 1, R<sup>1</sup> and R<sup>3</sup> are hydrogen and R<sup>2</sup> is 1-piperidiny, is a nuclear regulatory molecule. Raloxifene has been shown to bind to the estrogen receptor and was originally thought to be a molecule whose function and pharmacology was that of an anti-estrogen in that it blocked the ability of estrogen to activate uterine tissue and estrogen dependent breast cancers. Indeed, raloxifene does block the action of estrogen in some cells; however in other  
10 cell types, Raloxifene activates the same genes as estrogen does and displays the same pharmacology, e.g., osteoporosis, hyperlipidemia. As a result, raloxifene has been referred to as an anti-estrogen with mixed agonist-antagonist properties. The unique profile which raloxifene displays and differs from that of estrogen is now thought to be due to the unique activation and/or suppression of various gene functions by the raloxifene-estrogen receptor complex as opposed to the activation and/or suppression of genes by the estrogen-estrogen receptor complex. Therefore, although Raloxifene and estrogen utilize and compete for the same receptor, the  
15 pharmacological outcome from gene regulation of the two is not easily predicted and is unique to each.

Generally, the compound is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and may be formulated  
20 as sustained release dosage forms and the like.

The compounds used in the methods of the current invention can be made according to established procedures, such as those detailed in U.S. Patent Nos. 4,133,814, 4,418,068, and 4,380,635 all of which are incorporated by reference herein. In general, the process starts with a benzo[b]thiophene having a 6-hydroxyl group and a 2-(4-hydroxyphenyl) group. The starting compound is protected, acylated, and deprotected to form  
25 the formula I compounds. Examples of the preparation of such compounds are provided in the U.S. patents discussed above. Substituted phenyl includes phenyl substituted once or twice with C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, hydroxy, nitro, chloro, fluoro, or tri(chloro or fluoro)methyl.

The compounds used in the methods of this invention form pharmaceutically acceptable acid and base addition salts with a wide variety of organic and inorganic acids and bases and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention.  
30 Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, β-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, chloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propionate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like. A preferred salt is the hydrochloride salt.  
45

The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid. The reactants are generally combined in a mutual solvent such as diethyl ether or benzene. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

Bases commonly used for formation of salts include ammonium hydroxide and alkali and alkaline earth metal hydroxides, carbonates, as well as aliphatic and primary, secondary and tertiary amines, aliphatic diamines. Bases especially useful in the preparation of addition salts include ammonium hydroxide, potassium carbonate, methylamine, diethylamine, ethylene diamine and cyclohexylamine.  
50

The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared to the compound from which they are derived, and thus are often more amenable to formulation as liquids or emulsions.  
55

Pharmaceutical formulations can be prepared by procedures known in the art. For example, the compounds can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Examples of excipients, diluents, and carriers that are suitable for such

formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols.

The compounds can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

The particular dosage of a compound of formula I required to inhibit the breast disorders according to this invention will depend upon the severity of the condition, the route of administration, and related factors that will be decided by the attending physician. Generally, accepted and effective daily doses will be from about 0.1 to about 1000 mg/day, and more typically from about 50 to about 200 mg/day. Such dosages will be administered to a subject in need of treatment from once to about three times each day, or more often as needed to effectively treat the symptoms.

It is usually preferred to administer a compound of formula I in the form of an acid addition salt, as is customary in the administration of pharmaceuticals bearing a basic group, such as the piperidino ring. It is also advantageous to administer such a compound by the oral route. For such purposes the following oral dosage forms are available.

#### Formulations

In the formulations which follow, "Active ingredient" means a compound of formula I.

##### Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The ingredients are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules.

Examples of specific capsule formulations of raloxifene that have been made include those shown below:

##### Formulation 2: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	1
Starch, NF	112
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

##### Formulation 3: Raloxifene capsule

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Ingredient	Quantity (mg/capsule)
Raloxifene	5
Starch, NF	108
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 4: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	10
Starch, NF	103
Starch flowable powder	225.3
Silicone fluid 350 centistokes	1.7

Formulation 5: Raloxifene capsule

Ingredient	Quantity (mg/capsule)
Raloxifene	50
Starch, NF	150
Starch flowable powder	397
Silicone fluid 350 centistokes	3.0

The specific formulations above may be changed in compliance with the reasonable variations provided.

A tablet formulation is prepared using the ingredients below:

Formulation 6: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Cellulose, microcrystalline	0 - 650
Silicon dioxide, fumed	0 - 650
Stearate acid	0 - 15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.1 - 1000 mg of active ingredient are made up as follows:

Formulation 7: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.1 - 1000
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.1 - 1000 mg of medicament per 5 mL dose are made as follows:

**Formulation 8: Suspensions**

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

**TEST PROCEDURE**

**ASSAY 1**

Five to fifty women are selected for the clinical study. The women have a history of a breast disorder as described herein, but are in good general health. Because of the subjective nature of these disorders, the study has a placebo control group, i.e., the women are divided into two groups, one of which receive the active agent of this invention and the other receive a placebo. Women in the test group receive between 50-200 mg of the drug per day by the oral route. They continue this therapy for 3-12 months. Accurate records are kept as to the status of the breast disorders in both groups and at the end of the study these results are compared. The results are compared both between members of each group and also the results for each patient are compared to the symptoms reported by each patient before the study began.

Utility of the compounds of the invention is illustrated by the positive impact they have on the disorder or a symptom or symptoms thereof when used in a study as above.

**ASSAY 2**

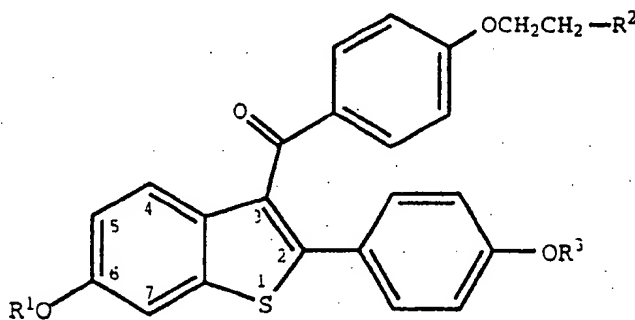
Between three and twenty male patients suffering from gynecomastia or galactorrhea are selected. Initial

measurement of breast size and evidence of lactation is noted. The patients receive 30-100mg of an active compound of this invention per day as a single or divided dose via the oral route. This treatment is continued for 3-12 months. At appropriate intervals further measurements of breast size or evidence of lactation are being made.

Utility of the compounds of the invention is illustrated by the positive impact on the disorder or its symptoms.

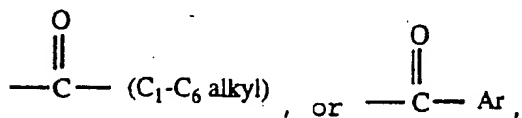
# Claims

1. The use of a compound having the formula



(I)

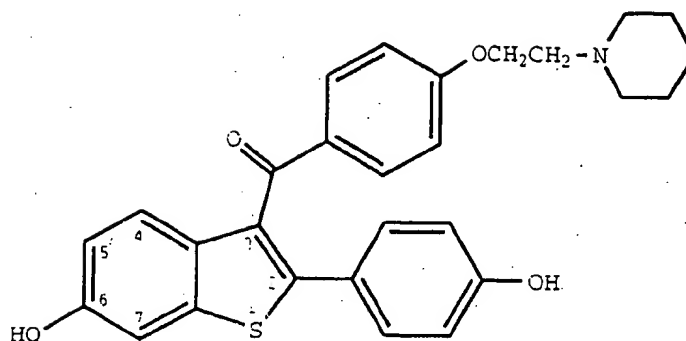
wherein R¹ and R³ are independently hydrogen, -CH₃,



wherein Ar is optionally substituted phenyl;

R² is selected from the group consisting of pyrrolidino and piperidino; or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament useful for inhibiting breast disorders.

2. The use of Claim 1 wherein said compound is the hydrochloride salt thereof.
3. The use of Claim 1 wherein said medicament is prophylactic.
4. The use of Claim 1 wherein said compound is



or its hydrochloride salt.

5. The use of Claim 1 wherein said breast disorder is selected from gynecomastia, galactorrhea, non-fibrocystic, non-cancerous mastodynia and mastopathy.





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# EUROPEAN SEARCH REPORT

Application Number  
EP 94 30 9477

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl. 6)
X	US-A-4 895 715 (NERI ET AL.) 23 January 1990 * whole document in particular col.3 line 35-col.4 line 1 *	1-5	A61K31/445 A61K31/40 A61K31/38
X	WO-A-93 10113 (TEIKOKU HORMONE) 27 May 1993 * abstract * * formula B *	1-5	
X	LIFE SCIENCE, vol. 32, no.25, 1983 pages 2869-2876, J.A. CLEMENS ET AL. 'EFFECTS OF A NEW ANTIESTROGEN, KEOXIFEN (LY156758), ON GROWTH OF CARCINOGEN-INDUCED MAMMARY TUMORS AND ON LH AND PROLACTIN LEVELS' * the whole document *	1-4	
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 27, no.8, 1984 pages 1057-1066, C.D. JONES ET AL. 'ANTIESTROGENS.2.'	1-4	TECHNICAL FIELDS SEARCHED (Int.Cl. 6)
Y	* the whole document *	5	A61K
D,X D,Y	US-A-4 418 068 (JONES) 29 November 1983 * abstract; claims *	1-4 5	
Y	METABOLISM, vol. 35, no.8, 1986 pages 705-708, L.N. PARKER ET AL. 'TREATMENT OF GYNECOMASTIA WITH TAMOXIFEN' * the whole document *	5	
		-/--	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 23 March 1995	Examiner Hoff, P
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>A : member of the same patent family, corresponding document</p>			

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# EUROPEAN SEARCH REPORT

Application Number  
EP 94 30 9477

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	ARCH. GYNECOL., vol. 237, 1985 page 342 A. FIGUEIRA ET AL. 'THE TREATMENT OF SEVERE MASTALGIAS WITH ANTI-ESTROGEN THERAPY' * the whole document *	5	
Y	THE LANCET, vol. 1, no.8476, 1986 pages 287-288, I.S. FENTIMAN ET AL. 'DOUBLE-BLIND CONTROLLED TRIAL OF TAMOXIFEN THERAPY FOR MASTALGIA' * the whole document *	5	
D,X	US-A-4 133 814 (JONES ET AL.) 9 January 1979 * abstract; claims *	1-4	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 23 March 1995	Examiner Hoff, P
<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document</p>			

EPF FORM 1503 (01/91) (P.O. 01/91)